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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/813,965	03/31/2004	Robert Falotico	CRD-5073 NP	7706

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EXAMINER	
KIM, JENNIFER M	

ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
07/11/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/813,965	FALOTICO ET AL.	
	Examiner	Art Unit	
	Jennifer Kim	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5,9 and 10* is/are pending in the application.

4a) Of the above claim(s) *9 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4 and 5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/11/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed April 9, 2008 have been received and entered into the application.

Applicants' amendment necessitated additional rejection presented in this Office Action.

Response to Arguments

Applicants' arguments filed April 9, 2008 have been fully considered but they are not persuasive. Applicants argue that Sehgal discloses an injectable composition of rapamycin that comprise no vitamin E and no ethanol in the final product and relies on non-ionic surfactants such as Cremophor, but the claimed invention, ethanol is present in the amount of 0.5 percent up to 2.0 percent. Further, Myers teaches a solid solution of vitamin E TPGS and a pharmaceutical agent. Moreover, Copperstone adds nothing with respect to the rejection of claim 1. This is not found to be persuasive because the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Sehgal teaches an injectable

composition of rapamycin, suitable for intravenous administration with effective concentration of rapamycin with nonionic surfactants and solvents such as ethanol while Myers teaches TPGS is known as a surface active agent derived from a natural source of vitamin E and enhances bioavailability of the active drug. Therefore, it would have been obvious to one of ordinary skill in the art to incorporate vitamin E TPGS in Sehgal's rapamycin formulation because Sehgal teaches that various surfactants can be employed in such formulation and because TPGS is well known surfactant utilized in a pharmaceutical formulations. There is a motivation to incorporate surfactants such TPGS to Sehgal's rapamycin formulation be because it enhances bioavailability of the active drug. With regard to Myers teaching of a solid solution, it is noted that Myers reference is cited only to show that TPGS is well known as a surface active agent and a bioavailability enhancer. With regard to the amount of ethanol to be employed such is obvious because Sehgal teach that a solvent such as ethanol can be employed in the rapamycin formulation and some or all of the ethanol content can be removed once the dissolution of rapamycin takes place. Therefore, to optimize the amount of "some or all" of the ethanol content encompassing Applicants' amounts set forth in claim 1 is obvious and it is clearly taught and suggested by Sehgal. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4 and 5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The range of ethanol content "**about 0.5 percent** to less than two percent" lack literal support in the specification as originally filed. This is a New Matter Rejection.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sehgal (EP 0041795 A2) of record in view of Myers (U.S.Patent No. 5,891,845).

Sehgal teaches an injectable composition of rapamycin, suitable for intravenous administration comprising about 1 to 20mg/ml of rapamycin composition and nonionic surfactants. (page 19, claim 1). This concentration range encompasses Applicants' range set forth in claims 1 and 3. Sehgal teaches that the rapamycin composition is prepared by dissolving rapamycin in an organic solvent which is capable of dissolving rapamycin and is miscible with the nonionic surfactant such as ethanol, and adding the nonionic surfactant, if required, removing some or all of the organic solvent, and adding water. (page 6, line 4- page 7, line 5). Sehgal illustrates the preparation of an injectable rapamycin composition by removing ethanol by evaporation. (page 8, example 1, claim 7). Sehgal teaches that various surfactant can be employed in the composition. (page 3, claim 9).

Sehgal do not teach the amount of ethanol and vitamin E TPGS set forth in claim 1.

Myers teaches TPGS is known as a surface active agent derived from a natural source of vitamin E and believed to be a bioavailability enhancer and utilized in various formulations. (column 7, lines 13-65).

It would have been obvious to one of ordinary skill in the art to incorporate vitamin E TPGS in Sehgal's rapamycin formulation because Sehgal teaches that various surfactants can be added in the formulation and because Myers teaches that TPGS is known surfactant utilized in various formulations. One would have been motivated to make such modification in order to achieve enhanced bioavailability of rapamycin by adding surfactant such as TPGS taught by Myers as a bioavailability

enhancing surfactant. There is a reasonable expectation of successfully formulating rapamycin together with TPGS because Sehgal teach that various surfactants can be employed in rapamycin formulation and vitamin E-TPGS provides enhanced bioavailability of rapamycin. With regard to an ethanol content of less than 2%, such is obvious because Sehgal illustrates removing ethanol by evaporation upon the dissolution of rapamycin in the process of preparing the injectable formulation of rapamycin. Sehgal teaches that some or all of the ethanol content can be removed once the dissolution of rapamycin takes place. Therefore, the ethanol content of less than 2% is encompassed by the evaporation step taught by Sehgal et al.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sehgal (EP 0041795 A2) of record in view of Myers (U.S.Patent No. 5,891,845) as applied to claims 1 and 4 above, and further in view of Cooperstone et al. (U.S.Patent No. 7,060,709 B2) of record.

The teachings of Sehgal and Myers as applied as before.

Sehgal and Myers do not teach CCI-779.

Copperstone et al. teach that CCI-779 is a rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid and can be formulated in an injectable composition. (abstract, column 1, lines 61-67). Cooperstone et al. teach that that use of a surfactant with diluents is advantageous in the CCI-779 parenteral formulation because it prevents precipitation of CCI-779 upon dilution with aqueous infusion solutions or blood. (column 7, lines 7-14).

It would have been obvious to one of ordinary skill in the art to employ rapamycin compound such as CCI-779 in Sehgal's formulation as modified by Myers because Copperstone et al. teach that CCI-779 is a rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid and can be formulated in an injectable composition. One would be motivated to make such modification in order to achieve an expected benefit of stability of CCI-779 with surfactant and diluents contained in Sehgal's composition as modified by Myers preventing precipitation of CCI-779.

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 103.

THIS ACTION IS MADE FINAL. Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 571-272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer Kim/
Primary Examiner, Art Unit 1617

Jmk
July 8, 2008